Grapefruit juice–drug interactions

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The novel finding that grapefruit juice can markedly augment oral drug bioavailability was based on an unexpected observation from an interaction study between the dihydropyridine calcium channel antagonist, felodipine, and ethanol in which grapefruit juice was used to mask the taste of the ethanol. Subsequent investigations showed that grapefruit juice acted by reducing presystemic felodipine metabolism through selective post-translational down regulation of cytochrome P450 3A4 (CYP3A4) expression in the intestinal wall. Since the duration of effect of grapefruit juice can last 24 h, repeated juice consumption can result in a cumulative increase in felodipine AUC and C_{max}. The high variability of the magnitude of effect among individuals appeared dependent upon inherent differences in enteric CYP3A4 protein expression such that individuals with highest baseline CYP3A4 had the highest proportional increase. At least 20 other drugs have been assessed for an interaction with grapefruit juice. Medications with innately low oral bioavailability because of substantial presystemic metabolism mediated by CYP3A4 appear affected by grapefruit juice. Clinically relevant interactions seem likely for most dihydropyridines, terfenadine, saquinavir, cyclosporin, midazolam, triazolam and verapamil and may also occur with lovastatin, cisapride and astemizole. The importance of the interaction appears to be influenced by individual patient susceptibility, type and amount of grapefruit juice and administration-related factors. Although *in vitro* findings support the flavonoid, naringin, or the furanocoumarin, 6′,7′-dihydroxybergamottin, as being active ingredients, a recent investigation indicated that neither of these substances made a major contribution to grapefruit juice-drug interactions in humans.

Keywords: grapefruit juice, drug interaction, CYP3A4, intestinal drug metabolism, pharmacokinetics, pharmacodynamics

Introduction

The opportunity for a food-drug interaction is an everyday occurrence. The interaction can be particularly important when total drug absorption is altered. Recently, a chance observation led to the finding that grapefruit juice can markedly increase the oral bioavailability of a number of medications [1]. This article retraces discovery of this novel interaction and reviews the mechanism of action, summaries both studied and predicted medications for an interaction, discusses possible active ingredient(s) in the juice and considers clinical implications.

Discovery

Originally, a study was designed to test for an interaction between ethanol and the dihydropyridine calcium channel antagonist, felodipine [2], an analogue of nifedipine. Grapefruit juice was chosen to mask the taste of the ethanol following an assessment of every juice in a home refrigerator one Saturday evening. White grapefruit juice, particularly double-strength juice (single dilution of frozen concentrate), was the most effective. The combination of a non-intoxicating dose of ethanol and felodipine resulted in lower standing blood pressure and a high frequency of orthostatic hypotension compared with felodipine alone in patients with untreated borderline hypertension [2]. Although plasma felodipine concentrations were not different between treatments, they were several-fold higher than observed in other pharmacokinetic investigations with the same dose of drug. A systematic examination for obvious possible causes, such as incorrect dose or drug assay problems, did not resolve this discrepancy and eventually resulted in a pilot project in a single volunteer to judge the role of the juice. Plasma felodipine concentrations were more than five-fold greater with grapefruit juice compared with water (Figure 1).

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Mechanism

Felodipine disposition and metabolism

Felodipine has been the most extensively studied probe for grapefruit juice—drug interactions. Normally, felodipine is completely absorbed from the gastrointestinal tract following oral administration [3]. However, it undergoes high presystemic (first-pass) metabolism resulting in low absolute bioavailability averaging 15% [3] but ranging from 4% to

36% among individuals [4]. Both the gut wall and the liver appear responsible for presystemic felodipine elimination [5] (Figure 2).

Felodipine has a single primary metabolite, dehydrofelodipine [6], generated by cytochrome P450 3A4 (CYP3A4; Figure 3) [7]. Dehydrofelodipine is inactive and oxidized by two secondary pathways. The major secondary metabolite, M3, is also produced by CYP3A4 [8]. Apical enterocytes of the small bowel and hepatocytes of the liver both contain CYP3A4 [9, 10]. The content of CYP3A4 in both tissues

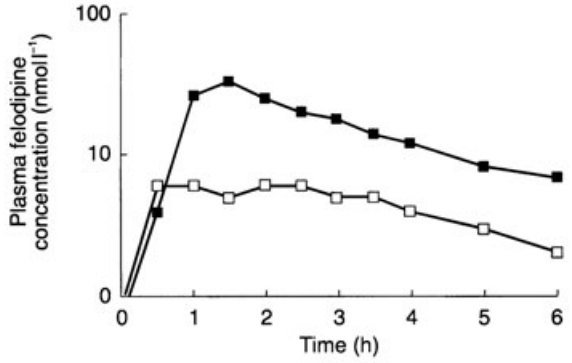


Figure 1 Plasma felodipine concentration-time profile from the pilot study in which the effect of grapefruit juice was evaluated in one of the authors (DGB). Felodipine 5 mg regular tablet was administered with 350 ml double-strength grapefruit juice (■) or water (□).

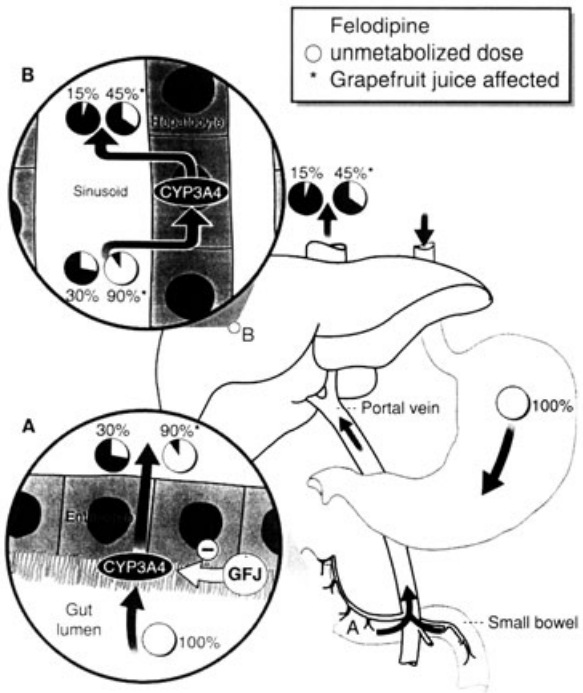


Figure 2 Sequential presystemic felodipine metabolism by CYP3A4 in apical enterocytes of the small bowel (A) and the hepatocytes of the liver (B) in the absence and presence of grapefruit juice. The percent of unmetabolized felodipine is presented before and after passage through the gut wall and the liver. Grapefruit juice selectively inactivated CYP3A4 in apical enterocytes.

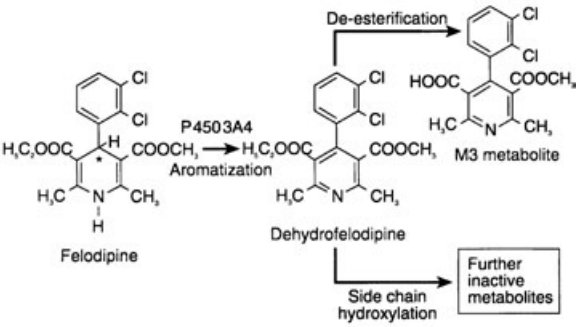


Figure 3 Pathways of felodipine metabolism.

ranges at least 10-fold among individuals and appears to be regulated independently of the other [11].

Grapefruit juice effects

The first report of this interaction revealed that grapefruit juice, but not orange juice, tripled mean plasma felodipine area under the curve (AUC) compared to water in borderline hypertensive patients [12]. Blood pressure reduction, heart rate increase and frequency of vasodilatation-related adverse events were also greater. Grapefruit juice markedly elevated plasma peak felodipine concentration (C_{max}) but did not alter systemic felodipine elimination half-life ($t_{1/2}$) [12]. Since grapefruit juice did not change intravenous felodipine pharmacokinetics [5], it indicates that the interaction with grapefruit juice resulted from inhibition of presystemic drug metabolism.

Grapefruit juice reduced dehydrofelodipine/felodipine AUC ratio and increased absolute dehydrofelodipine AUC [1, 12]. The decrease in the AUC ratio was compatible with inhibition of the primary metabolic pathway. The absolute increase in dehydrofelodipine AUC indicated that a subsequent metabolic pathway might also be inhibited and this was supported by measurements showing that the M3 metabolite AUC was reduced [8]. Thus, grapefruit juice appeared to inhibit CYP3A4, an important isozyme of cytochrome P450 since it oxidizes a broad range of drugs and xenobiotics [13], with predominant and perhaps exclusive action on presystemic drug elimination.

Recently, the effect of grapefruit juice on drug metabolizing enzymes of the small bowel and liver was reported in an *in vivo* investigation in humans [14]. Grapefruit juice consumption for 5 days caused a mean 62% reduction of small bowel enterocyte CYP3A4 and CYP3A5 protein content associated with a greater than 3- and 5-fold increase in felodipine AUC and C_{max}, respectively. In contrast, liver CYP3A4 activity, as measured by the erythromycin breath test, and colon CYP3A5 protein content were not altered. Also, intestinal CYP2D6 and CYP1A1 protein content were not affected. Although these changes were measured after 5 days of grapefruit juice, preliminary data also showed that small bowel CYP3A4 can be markedly reduced 4 h after a single glass of juice. Consequently, it was concluded that grapefruit juice acted by selectively inhibiting CYP3A isozymes of the small bowel to cause greater felodipine oral bioavailability.

Decreased expression of CYP3A isoforms by grapefruit

juice implied that the interaction was not simple competition for substrate metabolism. Since small bowel CYP3A4 mRNA was not changed [14], grapefruit juice likely decreased CYP3A4 protein content by a post-transcriptional mechanism, possibly involving accelerated CYP3A4 degradation through mechanism-based enzyme inhibition. Thus, the return of CYP3A4 activity would require *de novo* enzyme synthesis which could result in prolonged effect of grapefruit juice.

The duration of activity of grapefruit juice has been studied. In one study, consumption of a single glass (200 ml) of juice at various time intervals before felodipine showed that the extent of increase in felodipine AUC and C_{max} was maximal between simultaneous and 4 h previous juice administration with drug [15]. Then, the magnitude of the interaction declined slowly with increasing time interval between grapefruit juice and felodipine administration. The half-life of effect of grapefruit juice was estimated at 12 h. Higher felodipine C_{max} was still evident when grapefruit juice was consumed 24 h before felodipine. In another investigation, the effect of routine grapefruit juice consumption was evaluated [14]. One glass (250 ml) of grapefruit juice augmented mean felodipine AUC and C_{max} to 267% and 345%, respectively, of that compared with water. Grapefruit juice three times daily with meals for 5 days further increased felodipine AUC and C_{max} to 345% and 538% of that compared with water showing a cumulative effect of the juice.

The magnitude of the interaction was highly variable among individuals ranging from no change to six-fold greater plasma felodipine AUC and C_{max} with grapefruit juice compared with water under single dose conditions [1, 8, 14, 16]. However, it was reproducible within individuals following repeat testing and thus, dependent on factors inherent to the individual [16]. Grapefruit juice reduced small bowel CYP3A4 content contingent upon pretreatment levels [14]. Individuals with the highest small bowel CYP3A4 content before grapefruit juice had the largest reduction in CYP3A4 and highest increase in felodipine C_{max} with grapefruit juice. Consequently, individual disparity in the magnitude of interaction with grapefruit juice appears at least partially explained by innate differences in baseline small bowel CYP3A4 protein content.

Drugs interacting with grapefruit juice

Summary of studied drugs

Most medications investigated for an interaction with grapefruit juice are substrates for CYP3A4 (Table 1). The most extensively studied are the dihydropyridine calcium channel antagonists. In addition to felodipine [5, 8, 12, 14–18], these include nisoldipine [19], nimodipine [20], nicardipine [21], nitrendipine [22, 23], nifedipine [12, 24–26], and amlodipine [27, 28], which have similar pathways of metabolism [6], but vary markedly in absolute oral bioavailability dependent upon extent of presystemic drug elimination [29].

Based on the previous discussion, it would be expected that a dihydropyridine with low inherent oral bioavailability would have a greater magnitude of the interaction with grapefruit juice than with a dihydropyridine with normally high oral bioavailability. Nisoldipine [19] and amlodipine [27] are examples of dihydropyridines with very low and very high innate oral bioavailability, respectively. Mean (range) drug C_{max} for nisoldipine was 406% (107%–836%) [19] and for amlodipine was 115% (79%–165%) [27] with grapefruit juice compared with water. Thus, nisoldipine did have a much greater fold increase of plasma drug concentrations compared with amlodipine. Furthermore, inter-individual variability of the interaction was larger for nisoldipine which highlights the unpredictability of the interaction among individuals for dihydropyridines with low oral bioavailability.

All dihydropyridines, apart from nifedipine, have a chiral centre with activity primarily residing with a particular enantiomer [6]. The relevance of an interaction with grapefruit juice then depends mostly on the magnitude of increase of the more active enantiomer. For nitrendipine, the S-enantiomer possesses the activity [30, 31]. Grapefruit juice produced proportional enhancement of both enantiomers indicating that the increase in plasma total nitrendipine concentration was predictive of the pharmacodynamic extent of interaction [22]. For nicardipine, the S-enantiomer has one-third the activity of the R-enantiomer [32]. Grapefruit juice augmented S-nicardipine AUC and C_{max} by 1.5-and 1.2-fold more than R-nicardipine demonstrating that the effect on plasma total nicardipine concentration may slightly overestimate associated clinical consequences [21]. The S-enantiomer of non-dihydropyridine calcium channel antagonist, verapamil, has at least 10 times the dromotropic activity compared with the R-enantiomer [33]. Grapefruit juice produced less than a doubling of mean plasma total verapamil AUC and C_{max} [34]. However, first degree heart block (PR interval >240 ms) was observed in only subjects (4 of 24) who received verapamil with grapefruit juice. Although inter-subject variation of the interaction was not reported, grapefruit juice may preferentially augment S-verapamil and thus, the increase in plasma total verapamil concentrations would underestimate the importance of the interaction.

The non-sedating antihistamine, terfenadine, undergoes nearly complete presystemic elimination mediated by CYP3A4 [35, 36] and is often not detected in plasma. One of the primary metabolites, terfenadine carboxylate, accounts for the activity [36]. Terfenadine, like quinidine, is a potent blocker of myocyte delayed rectifier potassium current whereas terfenadine carboxylate is devoid of this effect [37–39]. Plasma terfenadine concentrations can be measured with overdose, liver disease or inhibition of CYP3A4 metabolism by concomitant administration of ketoconazole, erythromycin or itraconazole and are associated with prolongation of the QTc interval and development of a serious ventricular tachyarrhythmia, torsades de pointes [40–52]. Approximately 125 deaths linked to terfenadine have been reported [53]. Controlled clinical investigations have shown that grapefruit juice augmented plasma terfenadine concentrations [54–57]. A small increase in the QTc interval was demonstrated [54, 55]. The magnitude of the interaction was similar to that produced by itraconazole or erythromycin [56]. A fatality has been attributed to terfenadine toxicity after consuming the drug with grapefruit

Bioavailability	*Medication*	*Drug AUC*	*Drug C_{max}*
<5%	Nisoldipine [19]	**198**	**406**
	Nimodipine [20]	**151**	124
	Terfenadine [54–57]	**249**	343
	Saquinavir [73]	**150–220**	—
15–20%	Felodipine [5, 8, 12, 14–18]	**145–345**	**170–538**
	Nicardipine [21]	**134–196**	**125–153**
	Nitrendipine [22, 23]	**140–206**	140–**199**
	Propafenone [79]	133	123
	17β-oestradiol [82]	116	131
30–40%	Cyclosporin [65–71]	108–**162**	104–**132**
	Diltiazem [80]	110	102
	Ethinylestradiol [81]	128	137
	Midazolam [62]	**152**	**156**
	Triazolam [63]	**148**	**130**
	Verapamil [34]	**143**	**161**
60%	Nifedipine [12, 24–26]	**134–203**	104–**194**
70%	Quinidine [75]	108	93
>80%	Acenocoumarol [74]	98	—
	Amlodipine [27, 28]	108–116	115
	Prednisone [69]	150	139
	Theophylline [76]	103	97

Table 1 Innate oral drug bioavailability and mean relative drug AUC and C_{max} with grapefruit juice compared with control (%) among studies.

Statistically significant increases in drug AUC and C_{max} are indicated in bold. All medications are substrates for CYP3A4 except for prednisone and theophylline.

juice [58]. Since there appears to be little benefit from taking grapefruit juice with terfenadine and there is the potential for a serious adverse interaction, regardless of the frequency of occurrence, it seems wise to advise against grapefruit juice consumption during therapy with terfenadine.

Midazolam and triazolam are two ultra-short acting benzodiazepine hypnotics with high presystemic drug metabolism. For midazolam, a substantial portion of presystemic metabolism appears to occur in the small bowel [59, 60] and the major primary metabolite, 1′-hydroxymidazolam, is generated by CYP3A4 [61]. Grapefruit juice increased mean midazolam AUC and C_{max} by an estimated 41% selective decrease of prehepatic midazolam metabolism [62]. Psychometric tests showed greater patient impairment when oral midazolam was administered with grapefruit juice compared with water. Similarly, grapefruit juice augmented triazolam AUC and C_{max} to produce enhanced drowsiness [63].

Cyclosporin is the cornerstone of immunosuppression therapy following transplantation. Plasma cyclosporin concentrations must be maintained within a narrow range to achieve adequate immunosuppression without nephrotoxicity. However, cyclosporin possesses low and variable oral bioavailability. Although this has been attributed to poor drug solubility and diffusion characteristics, more recent work has supported presystemic cyclosporin metabolism as a factor [64]. In two studies of healthy volunteers, grapefruit juice produced mean oral cyclosporin AUCs which were 162% and 143% of that with water [65, 66]. Orange juice did not augment cyclosporin AUC [66]. Several studies were conducted in medically stable renal transplant patients [67–71]. Grapefruit juice was given with the patient's usual oral dose of cyclosporin to achieve steady state. The effect of grapefruit juice on cyclosporin pharmacokinetics varied among studies. Plasma cyclosporin AUC [68, 70, 71] and trough concentration [67, 70], which is commonly used during therapeutic drug monitoring, were augmented in some investigations. The largest mean interaction was a cyclosporin AUC and trough concentration with grapefruit juice that were 134% and 177%, respectively, of that compared with water [70]. There was more than a tripling in plasma trough cyclosporin concentration in at least one patient which undoubtedly is clinically important [71]. Because cyclosporin is very expensive, administration with grapefruit juice has been suggested as a technique to decrease drug costs [66]. However, the magnitude of the effect is variable among patients and the constancy of the interaction with repeat dosing has not been documented. Thus, concurrent administration of grapefruit juice cannot presently be recommended as a therapeutic strategy for such patients [72].

The anti-AIDS drug, saquinavir, belongs to a new class of agents known as protease inhibitors. Its very low bioavailability is in part due to presystemic metabolism by CYP3A4. A glass of regular-strength grapefruit juice augmented saquinavir AUC to 150% of that with water in HIV-negative volunteers [73]. Double-strength grapefruit juice enhanced saquinavir AUC to 220%. Since saquinavir has a wide therapeutic window, concomitant administration of grapefruit juice has been suggested as a strategy to increase saquinavir bioavailability. Although the magnitude of the interaction may be variable among patients, there appears to be only the potential for enhanced therapeutic benefit.

Grapefruit juice did not interact with a number of other medications. These include prednisone [69], acenocoumarol [74], quinidine [75] and theophylline [76]. This is not unexpected since these drugs already have high or almost

complete oral bioavailability. Prednisone and theophylline are also not substrates for CYP3A4. However, grapefruit juice did prolong the systemic elimination half-life of caffeine, a probe for CYP1A2 activity, and theophylline is metabolized by CYP1A2 [77]. This discrepancy for theophylline may be resolved by a recent report suggesting that grapefruit juice decreased caffeine elimination by inhibition of flavin-containing monooxygenase, a P450 independent system which does not appear to metabolize theophylline [78]. Other medications not showing an interaction with grapefruit juice include propafenone [79], diltiazem [80], ethinyloestradiol [81] and 17β-oestradiol [82]. Although they undergo presystemic metabolism, it appears that a substantial portion is by pathways not mediated by CYP3A4.

Drugs predicted to interact with grapefruit juice

The HMG-CoA reductase inhibitor, lovastatin, has been reported to produce a serious adverse skeletal muscle effect, rhabdomyolysis, when administered with drugs that inhibit CYP3A4 including itraconazole [83], erythromycin [84] and cyclosporin [85]. Lovastatin is a prodrug which normally undergoes extensive presystemic elimination [86]. Less than 5% of lovastatin is hydrolyzed to the pharmacologically active metabolite, lovastatin acid, with the majority biotransformed by other primary routes mediated by CYP3A4 [87]. Lovastatin and active metabolite AUCs were increased more than twenty-fold when administered with itraconazole suggesting the adverse effect has a pharmacokinetic basis [86]. Rhabdomyolysis has also been reported with simvastatin [88, 89] and pravastatin [90, 91]. Thus, a clinically important interaction may occur between grapefruit juice and lovastatin and possibly other HMG-CoA reductase inhibitors.

Prolonged QT interval, torsade de pointes and fatal arrhythmia have been reported with the gastrointestinal prokinetic agent, cisapride [92]. Adverse events occurred in conditions where plasma cisapride concentrations were elevated, particularly with concomitant administration of medications that inhibit CYP3A4. Cisapride normally undergoes presystemic metabolism by CYP3A4 resulting in a 40–50% absolute oral bioavailability [93]. Torsade de pointes has also been observed with the non-sedating antihistamine, astemizole, when administered with ketoconazole [94]. Astemizole has high presystemic elimination by three major metabolic routes to produce an estimated 3% oral bioavailability [95]. Unless medical condition warrants their use, it might be prudent to avoid the combination of grapefruit juice with cisapride or astemizole.

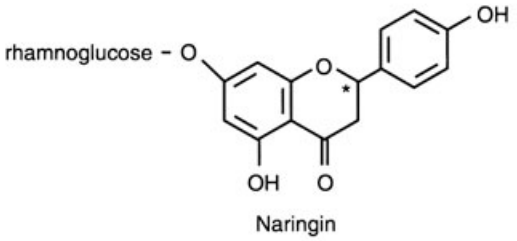
Active ingredient(s) in grapefruit juice

Identification of the active ingredient(s) in grapefruit juice would permit evaluation of this type of interaction with other foods. The apparently non-toxic active ingredient(s) in grapefruit juice might be also used commercially to dose orally drugs that are currently active only by the intravenous route because of complete presystemic metabolism involving CYP3A4 or to produce higher and more dependable drug bioavailability and clinical response among or within individuals [1]. In addition, because hepatic CYP3A4 activity does not appear to be altered by grapefruit juice [14], a major mechanism for systemic drug inactivation is not jeopardized. However, the persistence of hepatic CYP3A4 activity means that it would not likely be possible to produce complete oral drug bioavailability.

Flavonoids can inhibit drug oxidative metabolism [96]. Naringin (Figure 4) is the most prevalent flavonoid in grapefruit juice attaining relatively high concentrations (1 mmol l^{-1}) and is absent from orange juice [97] which did not produce the interaction [12, 66]. Naringin inhibited *in vitro* felodipine and nifedipine metabolism but was much less potent than its aglycone, naringenin [89, 99]. Although naringenin is not normally present in grapefruit juice [97], oral administration of grapefruit juice resulted in renal excretion of naringenin conjugates demonstrating *in vivo* formation of this potentially active species [100]. Also, naringenin was not detected in plasma and the total amount recovered in urine represented only a small percentage of the oral naringin dose in the juice [100], suggesting that naringenin has low systemic availability which is consistent with inhibition of drug metabolism localized to the small bowel. Nevertheless, commercially-available pure naringin, administered in the same amount as found in grapefruit juice, produced little or no increase in the plasma concentrations of felodipine [18] or nisoldipine [19].

A furanocoumarin, 6′,7′-dihydroxybergamottin, has been recently proposed as an active ingredient in grapefruit juice [101]. It and a related dimer caused a dose-dependent fall in CYP3A4 catalytic activity and immunoreactive CYP3A4 protein concentration in a Caco-2 cell culture model of human intestinal epithelium [102]. The concentration of 6′,7′-dihydroxybergamottin in grapefruit juice exceeded the IC_{50} for loss of CYP3A4 activity. CYP1A1 and CYP2D6 protein content were not affected. 6′,7′-Dihydroxybergamottin acted initially by competitive inhibition followed by mechanism-based inactivation of recombinant CYP3A4 consistent with the *in vivo* effects observed in humans.

Recently a study was reported that tested the hypothesis that naringin and/or 6′,7′-dihydroxybergamottin in grape-



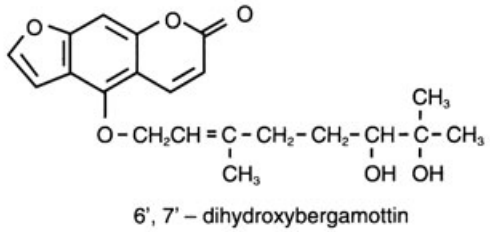


Figure 4 Chemical structure of naringin and 6′,7′-dihydroxybergamottin.

fruit juice are primarily responsible for the interaction with felodipine in humans [103]. The approach was to separate grapefruit juice by centrifugation and ultrafiltration into supernatant and particulate fractions. Then, the effect on oral felodipine pharmacokinetics of these fractions, of grapefruit juice containing a comparable amount of both fractions and of water were compared in healthy male volunteers. Because the amounts of naringin and 6′,7′-dihydroxybergamottin were found to be greater in the supernatant fraction (148 mg and 1.85 mg, respectively) than the particulate fraction (7 mg and 0.60 mg, respectively), it was postulated that the activity of the supernatant fraction would range from being greater than the particulate fraction to equivalent to the grapefruit juice. Felodipine AUC were higher with supernatant fraction and particulate fraction compared to water demonstrating that both fractions contained the active substance(s). However, the supernatant fraction had lower felodipine AUC than the particulate fraction. It was concluded that naringin and 6′,7′-dihydroxybergamottin are not the major active ingredients although they may contribute to the interaction. Recently, other furanocoumarins isolated from grapefruit juice were reported to inhibit *in vitro* human CYP3A [102, 104]. However, a final decision on their importance to the interaction must await results from *in vivo* testing in humans.

Therapeutic considerations

The clinical importance of any drug interaction depends on several factors. Of initial concern is the extent of change in drug pharmacokinetics. If there is a doubling or more of plasma drug concentration by grapefruit juice it should alert the physician or pharmacist to the possibility of enhanced, excessive or adverse drug effect. In the case of felodipine, doubling drug C_{max} with grapefruit juice produced twice the blood pressure reduction, heart rate increase and frequency of vasodilatation-related adverse events in borderline hypertensive patients [12]. Other medications which have demonstrated at least a doubling of plasma drug concentrations with grapefruit juice include dihydropyridines with low oral bioavailability, terfenadine [57] and saquinavir [73]. Furthermore, a lesser pharmacokinetic effect can be clinically important for a medication with a steep concentration (dose) response relationship or a narrow therapeutic window so that even a modest increase of plasma drug concentration could be translated into augmented or adverse effects. Thus, increases in plasma drug concentrations of cyclosporin [65–71], midazolam [62], triazolam [63] and verapamil [34] by grapefruit juice also appear pertinent.

Patient susceptibility is relevant to the interaction. Individuals that are highly dependent upon intestinal CYP3A4 activity for presystemic drug elimination, and perhaps especially patients with hepatic insufficiency, appear particularly sensitive for an interaction with grapefruit juice. Dihydropyridines like felodipine produce an antihypertensive effect not only dependent upon plasma drug concentration [105] but also on pretreatment blood pressure with the greatest drop in blood pressure occurring in patients with the highest pretreatment pressure [106]. This interaction appears particularly important for drugs of this class since the greater mortality of post-infarction patients and the suggestion of adverse outcome for hypertensives treated with immediate release dihydropyridines would argue that a rapid increase in plasma dihydropyridine concentration by grapefruit juice, even with the extended release formulation [5, 8, 14–16], may put these patients at risk of ischaemic complications [107–110]. Also, terfenadine with grapefruit juice may have increased chance of producing torsades de pointes in individuals with pre-existing prolonged QT interval.

Grapefruit juice type and amount are also important considerations. Commercial white grapefruit juice from frozen concentrate [5, 12, 14, 15, 27], diluted from concentrate [8, 16] or fresh frozen [18] has been shown to interact with felodipine. However, the magnitude of the interaction may differ among brands or even lots of juice depending upon the amount of active ingredient(s) present. Although double-strength grapefruit juice has been studied in some investigations [12, 17], it is evident that a single glass (200–250 ml) of regular-strength grapefruit juice can produce a several-fold increase in felodipine AUC and C_{max} [5, 8, 14–18]. This action of a commonly used portion of grapefruit juice highlights its practical importance.

Administration-related factors appear to affect the interaction. A marked response may occur with grapefruit juice and the initial drug dose and this could be greater following previous regular juice consumption. However, the cause could be erroneously attributed to inherent variation in normal drug effect among patients and overlooked as an interaction by patient, pharmacist or physician. It might be better recognized clinically in patients stabilized on a particular dose of a medication when grapefruit juice is added to the diet. Anecdotally, this has been observed with felodipine in two patients with increased accessibility to fresh grapefruit juice either while on winter vacation in warmer climates or following ripening of grapefruits in a backyard tree (personal communication). In contrast, a diminution of drug response may result following discontinuation of the juice.

Conclusions

A single glass of grapefruit juice has the potential to augment the oral bioavailability and to enhance the beneficial or adverse effects of a broad range of medications, even by juice consumed hours beforehand. Grapefruit juice acts by inhibiting presystemic drug metabolism mediated by CYP3A isoforms in the small bowel. The interaction appears particularly relevant for medications with at least a doubling of plasma drug concentration or with a steep concentration-response relationship or a narrow therapeutic index. Patients that appear particularly susceptible have high small bowel CYP3A4 content, hepatic insufficiency or a pre-existing medical condition which predisposes to enhanced, excessive or abnormal drug effects. Since grocers do not take a drug history, physicians, pharmacists and other health professionals should educate patients about consumption of grapefruit juice with medications.

Isolation of the active ingredient(s) may lead to identification of other foods producing this interaction or to its incorporation into pharmaceutical formulations. Further research is required to understand the interaction better

during routine grapefruit juice consumption, at amounts considered safe for administration with drugs and with different patient populations. Nevertheless, the serendipitous observation of increased plasma felodipine concentrations by grapefruit juice has provided fundamental new knowledge to improve pharmacotherapy and to stimulate research.

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